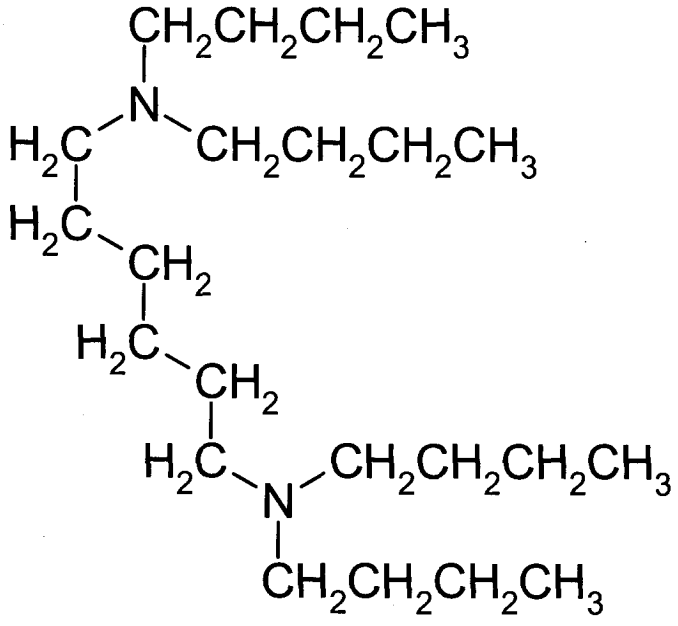
201-15838

# Tetrabutylhexamethylenediamine

## CAS Number 27090-63-7





## U.S. EPA HPV Challenge Program Submission

Submitted by:

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# Executive Overview

Tetrabutylhexamethylenediamine (TBHMD), CAS no. 27090-63-7, is an aliphatic tertiary diamine that is an intermediate in the manufacture of 1,6-bis(dibutylethylammonium)hexane hydroxide (BQAOH). BQAOH is used as a process aid in the manufacture of adiponitrile, which is a intermediate in Solutia's manufacturing process for nylon-6,6. A portion of the TBHMD is sold commercially and used for the same purpose. No other current commercial uses are known for this material. Solutia produces TBHMD at only one site and, except for the portion sold commercially, all TBHMD manufactured by Solutia is converted to BQAOH.

TBHMD is a clear oily liquid with an acrid odor. It has low volatility (estimated boiling point at 1013 hPa of 380°C and vapor pressure less than 0.015 hPa @ 25˚C) and is relatively insoluble in water (water solubility 120 mg/L). Because it is an amine, its solubility is pH dependent with greater solubility at lower (more acidic) values of pH.

In the environment, based on physicochemical properties, TBHMD has potential to bioaccumulate (Log $K_{o/w}$ > 3) and will distribute primarily to water and sediment where it will be subject to limited volatilization and assumed biodegradation under conditions favorable to bacteria. It is stable to hydrolysis but expected to react rapidly with atmospheric hydroxyl radicals with a half-life of less than an hour. Toxicity to aquatic species is unknown.

The acute oral toxicity of TBHMD is moderate with an $LD_{50}$ value of 380 mg/kg reported in a rat gavage studies. The dermal $LD_{50}$ in rabbits was found to be between 398 and 631 mg/kg and the material is corrosive to the skin. No inhalation data are available. Based on worker experience, the material is considered a skin sensitizer in humans.

A subchronic gavage study revealed that TBHMD is hepatotoxic in rats with a NOAEL of 2 mg/kg-day and a LOAEL (slight effects in females only) of 5 mg/kg-day. No other specific target organs were identified in this study.

Genetic toxicity data for TBHMD are not available. Although genotoxicity data are available for hexamethylenediamine and tributyl amine showing lack of genetic toxicity, neither is considered an adequate analog for TBHMD. Genotoxicity studies appropriate to the U.S. EPA-HPV Program are proposed.

Neither the reproductive nor the developmental toxicity of TBHMD has been studied experimentally. A reproductive and developmental toxicity screening study to investigate the potential of this material to affect reproductive and developmental parameters is proposed.

It is concluded that the available information for TBHMD adequately fills some of the HPV Program data elements. Studies have been proposed to investigate the biodegradation, aquatic toxicity, genotoxicity and reproductive/developmental toxicity of TBHMD.

# Testing Plan and Rationale

## Testing Plan in Tabular Format

| CAS No. 27090-63-7 TBHMD | Information Available? | OECD Study ? | GLP Study? | Supporting Information? | Estimation Method? | Acceptable? | Testing Recommended? | |
|---|---|---|---|---|---|---|---|---|
| **HPV Endpoint** | | | | | | | | |
| **Physical Chemical** | | | | | | | | |
| Melting Point | Y | N | N | N | N | N | N | |
| Boiling Point | Y | N | N | Y | Y | Y | N | |
| Vapor Pressure | Y | N | N | N | Y | Y | N | |
| Partition Coefficient | Y | N | N | N | Y | Y | N | |
| Water Solubility | Y | N | N | Y | N | Y | N | |
| **Environmental & Fate** | | | | | | | | |
| Photo-Degradation | Y | N | N | N | Y | Y | N | |
| Water Stability | Y | N | N | Y | Y | Y | N | |
| Transport | Y | N | N | N | Y | Y | N | |
| Biodegradation | N | N | N | Y | N | N | Y | |
| **Ecotoxicity** | | | | | | | | |
| Acute Fish | Y | N | N | N | Y | N | Y | |
| Acute Invertebrate | Y | N | N | N | Y | N | Y | |
| Acute Algae | Y | N | N | N | Y | N | Y | |
| **Toxicity** | | | | | | | | |
| Acute | Y | N | N | N | N | Y | N | |
| Repeated Dose | Y | N | Y | Y | N | Y | N | |
| Genetic Toxicology *"in vitro"* | N | N | N | N | N | N | Y | |
| Genetic Toxicology "*in vivo*" | N | N | N | N | N | N | Y | |
| Reproductive | N | N | N | N | N | N | Y | |
| Developmental | N | N | N | N | N | N | Y | |

# Introduction

(Tetrabutylhexamethylenediamine (TBHMD), CAS no. 27090-63-7, is an aliphatic tertiary diamine that is used as an intermediate in the manufacture of 1,6-bis(dibutylethylammonium)hexane hydroxide (BQAOH). BQAOH is used as a process aid in the manufacture of adiponitrile, which is primarily used as a intermediate in Solutia's manufacturing process for nylon-6,6. A portion of the TBHMD produced is sold commercially and used for the same purpose. No other current commercial uses are known for TBHMD.

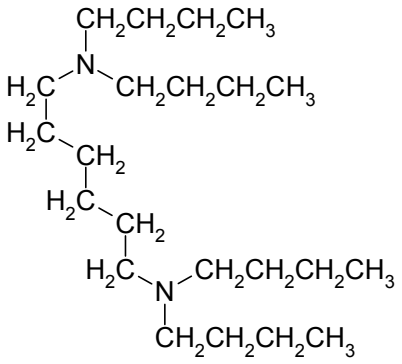
TBHMD is a clear oily liquid with an acrid odor. This material has low volatility (estimated boiling point at 1013 hPa of 380°C and vapor pressure less than 0.015 hPa @ 25˚C) and is relatively insoluble in pure water (water solubility 120 mg/L). Because it is an amine, its solubility is pH dependent with greater solubility at lower (more acidic) values of pH.

This material is batch-produced in a single reactor on a daily basis. Only the few workers converting hexamethylene diamine to BQAOH are potentially exposed to TBHMD as it serves only as an intermediate. Worker exposure is minimized by the use of closed systems and mandated personal protective equipment. Handling of TBHMD is restricted to trained personnel using personal protective equipment appropriate for handling a skin-corrosive liquid. Based on worker experience, the material is also considered a human skin sensitizer and appropriate procedures and equipment for handling a sensitizer are employed. Because of its acrid odor, the material possesses good warning properties. There is no established OSHA PEL or ACGIH TLV for TBHMD.

TBHMD is also known as (1):

- 1,6-Hexanediamine, N,N,N',N'-tetrabutyl- (8CI 9CI)
- N,N,N',N'-Tetrabutylhexamethylenediamine

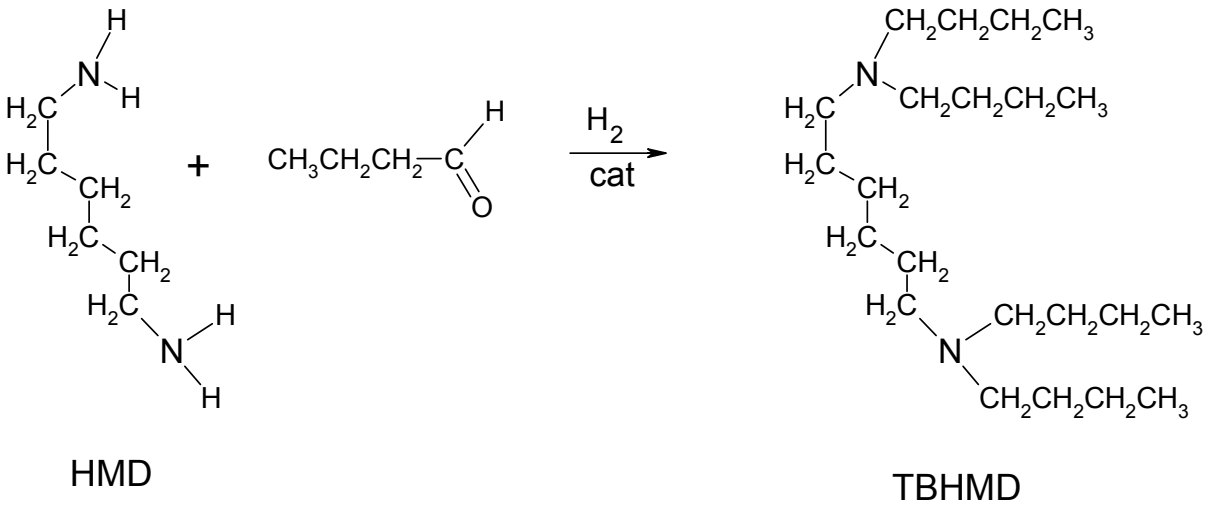
The chemical structure of TBHMD is shown below:



Tetrabutylhexamethylenediamine

## Chemistry of Manufacture

TBHMD is made by the reductive addition of 4 equivalents of butyraldehyde to hexamethylene diamine in the presence of a catalyst, as shown below:




HMD TBHMD

A limited number of studies relevant to the EPA HPV-Program have been conducted on TBHMD. These studies are briefly reviewed in this testing rationale document. Robust summaries have been prepared for key studies using the IUCLID format. The available data set satisfactorily fulfills some the data requirements for the EPA HPV Program. As data from appropriate surrogate chemicals were not found, studies are proposed to fill the additional HPV-recommended endpoints.

# Physicochemical, Fate and Aquatic Toxicity Information

## Physicochemical Data

Physicochemical data for TBHMD are available from the manufacturer and by estimation methods.

| Table 1: Physicochemical Properties of TBHMD | |
|---|---|
| Melting Point | < -18° C (2) |
| Boiling Point | ca. 380°C @ 1010 hPa (3)<br>83°C @ 2.9 hPa (2) |
| Vapor Pressure | < 0.015 hPa @ 25˚ C (3) |
| Partition Coefficient | Log $K_{o/w}$ = 4.56-7.59 (4) |
| Water Solubility | 1200 mg/L @ 25° C (2) |

These properties indicate that at ambient temperatures TBHMD is a low volatility liquid with limited water solubility in pure water. The EPIWIN estimated value of the partition coefficient is given as a range representing the free base form (7.59) and the diprotonated form (i.e two positive charges or $TBHMD^{++}$) and suggests that TBHMD will partition preferentially into fat; therefore, on the basis of only the octanol-water partition coefficient, TBHMD is considered to have potential for bioaccumulation. Actual bioaccumulation, however, is dependent upon pH, biodegradation and oxidative metabolism-depuration of TBHMD in organisms. As the $pK_a$ of tertiary amines is typically in the range of 10 to 11, most of the TBHMD will be in the protonated forms at the near neutral pH levels typically found in the environment and absorption by aquatic organisms may be limited.

**Recommendation:** No additional physicochemical studies are recommended. The available data fill the HPV required data elements.

## Environmental Fate and Pathways

TBHMD's photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced an estimated rate constant of 213 E-12 $cm^3$/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of

TBHMD with hydroxyl radical, the estimated half-life of TBHMD vapor in air is estimated to be approximately 0.6 hours (see accompanying robust summary for full details).

Water stability has not been quantitatively determined for TBHMD. No specific data were found for water stability of TBHMD or similar tertiary amines in the literature. Quantitative stability determinations (e.g. OECD 111) are not considered necessary for compounds containing only non-hydrolysable groups. Under these conditions, the SIDS manual states that consideration should be given to using an estimation method. Although amines are potentially hydrolysable (5), an estimate for this particular compound can be obtained using chemical principles. Assuming the reaction products of hydrolysis are the secondary amine and butanol, the enthalpy of the reaction can be calculated using standard bond energies. Although the entropy of the reaction cannot be easily estimated, estimates of the enthalpy of reaction and considerations of the free energy of the hydrolysis transition state indicate that hydrolysis is highly unlikely under environmental conditions. The hydrolytic half-life can therefore be reliably estimated at greater than one year. (6)

Aerobic biodegradation studies were not found for TBHMD. As the alkyl chains in TBHMD are not branched, it can be predicted that TBHMD will be biodegradable under aerobic conditions. Based on the slow rate of aerobic biodegradation of hexamethylenediamine (inherently biodegradable) (7) and the additional branching at the nitrogen centers, it is anticipated that TBHMD will not be "readily biodegradable" by the OECD definition. This information, combined with the limited uses of this material and disposal of waste material going to a wastewater treatment plant, suggests that an "inherent biodegradability" test (e.g. OECD 302 series) would be a more appropriate and valuable as an initial assay than a test of ready biodegradability (e.g. OECD 301 series).

Theoretical Distribution (Fugacity) of TBHMD in the environment was estimated using the MacKay EQC level III model set to estimate distribution after 100% release to water, which is considered the most probable scenario regarding the potential release of this material. The EPIWIN model was allowed to estimate fate parameters, however, actual water solubility and melting point were used in the estimate. Regarding materials such as TBHMD that ionize under environmental conditions, a problem with the EQC Level 3 model is that it cannot adequately handle materials that have an equilibrium of forms or states (such as electronic charge) under typical environmental conditions. For this reason, the EQC level 3 model was also run on the singly and doubly charged species as these are considered more representative of TBHMD in the normal environmental pH range. Details of the parameters used are in the accompanying robust summary for environmental distribution. Results of this estimate are shown below in Table 2.

As the ionization of the two tertiary amines is pH dependent and a dynamic process, it is difficult to obtain accurate estimates for environmental distribution. To better answer the question of which form of TBHMD predominates at environmental pH levels, the $pK_a$ for each species was estimated. Calculations indicate that the $pK_a$ for the ionization of the first nitrogen is about 10.2 and for the second nitrogen 9.5 (8). These estimated values indicate that the predominant species for at typical environmental pH levels with by the doubly charged form ($TBHMD^{++}$) and the material will remain primarily in water after water release. If the pH of the local

environment is changed due to excessive amounts of TBHMD causing an increase in pH, sediment distribution may become important.

| Environmental Compartment | Species Modeled | | |
|---|---|---|---|
| | TBHMD | $TBHMD^{+}$ | $TBHMD^{++}$ |
| ○ Air | < 0.01% | < 0.01% | < 0.01% |
| ○ Water | 10.5% | 29.8% | 88.5 % |
| ○ Soil | < 0.01% | < 0.01% | < 0.01% |
| ○ Sediment | 89.5% | 70.2% | 11.5 % |

**Table 2. EQC Modeling of Environmental Distribution of TBHMD after Release to Water.**

**Recommendation:** An aerobic biodegradation study according to the OECD 302 test guideline is recommended to complete the HPV information regarding fate.

## Ecotoxicity

No experimental aquatic toxicity data are available for TBHMD. An estimate of the potential toxicity of TBHMD was developed using the EPA ECOSAR program and is given in Table 3. The estimate was conducted for each of the three ionized forms of TBHMD as each form has a different $K_{o/w}$ and the toxicity estimate using ECOSAR is a function of the $K_{o/w}$. EPA has acknowledged that the aquatic toxicity of aliphatic amines has a strong pH dependency (9). The un-ionized form of the amine generally displays a greater toxicity than the ionized forms. The rationale for this effect is that uncharged species more readily cross biological membranes than charged forms. As the $pK_a$ of aliphatic amines is in the range of 9 to 11, they exist almost entirely in their charged form near neutral pH. On the other hand, as water solutions of aliphatic amines are basic, moderate to high concentrations of amines in weakly buffered water increase the pH and can theoretically exacerbate their aquatic toxicity. The estimates for the uncharged form of TBHMD also exceed the stated limitations of the aliphatic amines SAR model (limits: fish, $K_{o/w} < 6.0$; daphnids, $K_{o/w} < 5.0$; algae, $K_{o/w} < 7.0$) and are thus considered of lower reliability.

Another uncertainty surrounding the estimated for fish and invertebrates in the possibility that a specific mechanism of action may be operative since bi-tertiary amines, especially of this structural type, have been shown to act as blockers at nicotinic ganglia and neuromuscular junctions in mammals (10). It is thought that the di-cation (in this case represented by $TBHMD^{++}$) is the active form of bi-tertiary amines with nicotinic-blocking

action. As TBHMD is thought to be primarily in the di-cationic form at physiological pH, this type of activity is considered possible; thus, the neutral organics SAR model may be inadequate for certain organisms.

**Table 3: Comparative Estimated Aquatic Toxicity of TBHMD forms**

| Species | ECOSAR Prediction | | |
|---|---|---|---|
| | TBHMD | TBHMD$^{+}$ | TBHMD$^{++}$ |
| Fish, 96-hour $LC_{50}$ | 0.025 mg/L | 0.23 mg/L | 2.71 mg/L* |
| Daphnia, 48-hour $EC_{50}$ | 0.004 mg/L | 0.029 mg/L | -** |
| Algae, 96-hour $EC_{50}$ | 0.04 mg/L | 0.123 mg/L | -** |

* Estimate for 14-day fish

** ECOSAR would not provide estimate

**Recommendation:** Estimation methods for acute fish and invertebrate toxicity, and algal growth inhibition data are not considered to be of sufficient reliability to fill these HPV data points. It is proposed that these HPV endpoints be filled with OECD 201, 202 and 203 studies. As the test material is considered stable in solution, the use of static conditions under near-neutral (pH adjusted for the particular test protocol) with analytical determination of actual concentration is proposed.

# Health Effects

## Acute Toxicity

### Oral Exposure

A rat gavage study using six dose groups of rats of each sex has been conducted. An $LD_{50}$ of 380 mg/kg (95% confidence interval 330-430 mg/kg) was determined for TBHMD in this study. Deaths occurred from several hours to six days after administration with most occurring in four days. Clinical observations included reduced appetite and activity for three to nine days in survivors and increasing weakness, collapse and death in animals that did not survive the 14-day observation period. Upon gross necropsy, decedents showed hemorrhagic areas of the lungs, liver discoloration and gastrointestinal inflammation. (11)

### Dermal Exposure

A dermal acute toxicity study of undiluted TBHMD has been conducted using New Zealand albino rabbits and is describe in detail in the accompanying robust summary. The study used one rabbit at each of four dose levels from 251 to 1,000 mg/kg and the $LD_{50}$ was reported as being greater than 398 mg/kg and less than 631 mg/kg. The two rabbits that died on study (631 and 1,000 mg/kg) both expired on day one of the test. No cause of death was identified. Clinical sings in surviving rabbits were limited to reduced appetite and activity for three or nine days after dosing. (11)

**Recommendation:** No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet all requirements of current OECD guidelines, the data are consistent and the studies have been conducted by a scientifically defensible method. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional acute toxicity studies be conducted using this material.

## Repeat Dose Toxicity

Two oral-gavage repeated dose (28-day and 13-week duration) studies have been conducted with TBHMD. For the purposes of the HPV program, the 13-week study has been selected for presentation and summarization and is identified as the critical repeated-dose study for the HPV program because of the longer duration and because of the limitations of the 28-day study, which was identified as a range-finding study for the 13-week test.

The 13-week corn-oil gavage study was conducted with Charles River CD rats approximately 6 weeks old at initiation of dosing. Groups of 15 animals of each sex were dosed daily by corn-oil gavage at dose levels of 0, 2, 5 or 20 mg/kg body weight. Detailed observations were conducted once weekly and individual body weights and food consumption values were recorded weekly. Clinical pathology tests were run on 10 randomly selected rats/sex/group at 13 weeks of study and all test and control animals were sacrificed and necropsied after 13-weeks

of treatment. Administration of test substance for 13 weeks was associated with pathological changes in the liver of 20 mg/kg-day rats of each sex. Females appeared to be more affected. At 5 mg/kg-day, females showed slight liver pathology but males were not affected. Decrease in body weight gain, increase in leukocyte count, and increases in serum enzymes indicative of an hepatotoxic effect were also seen at the 20 mg/kg-day dose level. Although effects at 5 mg/kg-day were minor, it is considered a LOAEL and 2 mg/kg-day is considered the NOAEL for this study. (12)

**Recommendation:** No additional repeated-dose studies are recommended. The available data fill the HPV required endpoint for repeated-dose toxicity.

## Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one test sensitive for point mutation and one sensitive for chromosomal aberrations. No studies of TBHMD were found for either endpoint. The closest analogs with data that were identified were tributylamine (negative in the bacterial reverse mutation test and the mouse micronucleus test) and hexamethylenediamine (negative in the bacterial reverse mutation test and an *in vivo* chromosome aberration test). Although both of these similar materials lacked genotoxic activity, neither was considered a close enough analog to use as a high confidence surrogate for TBHMD.

**Recommendation:** It is proposed that the SIDS requirement for genetic testing be met by conducting a bacterial reverse mutation assay in accord with OECD-471 and an *in vitro* mammalian chromosome aberration test in accord with OECD-473.

## Reproductive Toxicity

No studies of the effect of TBHMD on reproduction were found. Reproductive organs of rats in the 13-week study were not affected, suggesting that TBHMD has no specific activity on reproduction. Although this limited information suggests lack of effect on reproductive function, it does not meet the HPV guidelines in the absence of additional data from a reproductive screening test or a developmental toxicity study.

**Recommendation:** A combined reproductive-developmental toxicity-screening test in recommended by the oral route using the OECG 421 testing guideline. If possible, dosing by gavage using a neutralized aqueous solution of test material is recommended to reduce gastric irritation and more closely mimic a repeated-dose exposure situation in man.

## Developmental Toxicity

Developmental toxicity studies of TBHMD were not found. It can be argued that as the test material is charged at physiologic pH and probably highly protein bound, it will not cross the placenta in concentrations that will selectivity affect the conceptus; however, the possibility that metabolites will cross the placenta and selectively affect the conceptus cannot be excluded in the absence of experimental data.

**Recommendation:** A combined reproductive-developmental toxicity-screening test in recommended by the oral route using the OECG 421 testing guideline. If possible, dosing by gavage using a neutralized aqueous solution of test material is recommended to reduce gastric irritation and more closely mimic a repeated-dose exposure situation in man.

# Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that the available information fills all of the HPV-Program data recommendations except for information related to biodegradation, aquatic toxicity, genetic toxicity and reproductive/developmental toxicity. Studies to fill these parameters are proposed as follows:

| Category | Endpoint | Test |
|---|---|---|
| Fate | Aerobic Biodegradation | OECD TG 302 |
| Aquatic Toxicity | Algal Inhibition | OECD TG 201 |
| | Daphnia Immobilization | OECD TG 202 |
| | Fish, Acute Toxicity Test | OECD TG 203 |
| Genotoxicity | Bacterial Reverse Mutation | OECD TG 471 |
| | *In vitro* Mammalian Chromosome Aberration Test | OECD TG 473 |
| Mammalian Toxicity | Reproduction/Developmental Toxicity Screening Test | OECD TG 421 |

**Table 4. Proposed Testing for TBHMD**

# References

1 Chemical Information System (CIS) file Database File: SANSS [Chemical Nomenclature, Formulas, Structures] CAS Registry Number: 27090-63-7, Source of Information: TSCA Inventory, CIS Record ID: SA-00177616

2 Measured value. Solutia Material Safety Data Sheet #027090637 version of Aug 31, 1998.

3 Estimated using MPBPWIN v1.40 program found in EPIWIN 3.05

4 Estimated using KOWIN v1.66 program found in EPIWIN 3.05 Range represents free base and diprotonated forms.

5 Harris, J.C. in Lyman W, Reehl, W and Rosenblat, D.(1990) Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington D.C.

6 Estimate conducted by Toxicology and Regulatory Affairs, December 2004. See robust summary for details.

7 IUCLID Dataset, Hexamethylenediamine (124-09-4), IUCLID 2000 European Chemicals Bureau 18-Feb-2000.

8 Values calculated by Toxicology and Regulatory Affairs using the online SPARC calculator at http://ibmlc2.chem.uga.edu/sparc. See Robust Summary for details of parameters.

9 See description of the aliphatic amines category in: Toxic Substances Control Act (TSCA) New Chemical Program Chemical Categories, October, 2002 (http://www.epa.gov/oppt/newchems/chemcat.htm).

10 Hill, SA, RFP Scott and JJ Savarese, Structure-activity relationships: from tubocurarine to the present day. In: Goldhill and Flynn eds Muscle Relaxants. London: Baillere Tindall, 1994: 317-348.

11 Younger Laboratories Inc, Final Report: Acute Toxicity Testing of N,N,N',N' Tetrabutylhexamethylene diamine project YO-75-165, 07-29-1975; sponsored by Monsanto Co.

12 International Research and Development Corp., Final Report: Tetrahexamethylenediamine, 13-Week Oral Toxicity Study in Rats. Monsanto Study IR 83-153, Sponsored by Monsanto. April 18, 1985.